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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,884	02/19/2004	Randy Scott	GHI-0007.US (GHDX-007)	2652

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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,884	SCOTT ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2008 and 16 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *104-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/2008;12/03/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/03/2008 has been entered.

Information Disclosure Statement

The Information Disclosure Statements filed on 10/13/2008 and 12/03/2008 have been considered.

Status

Claims 1-103 have been cancelled. New claims 104-113 have been added and are the only claims pending. Therefore, all previous rejections are withdrawn as moot, and all rejections herein are considered new rejections and are the only rejections pending in the application.

To the extent that Applicant's arguments filed 12/03/2008 apply to any new rejections, the arguments will be addressed following the rejections.

Claim Objections

Claim 104 is objected to for the following reason: it is missing a period at the end. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 104, 110, 112 and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipson et al (PNAS 86:9774-7 (1989)).

Lipson teaches a method for determining the expression level of a target gene in a tissue sample obtained from a human subject wherein an intron-specific probe is utilized (see abstract and page 9775, column 1, "Probes" and figure 1). Specifically, Lipson analyzes expression of the thymidine kinase in human fibroblasts (which is a tissue obtained from a human subject; see abstract and page 9774, column 2, first two paragraphs). Lipson's determination of the amount of TK hnRNA represents a determination of the "expression level" of the TK gene (just as measuring mature mRNA or protein level would also represent determinations of the "expression level" of the gene).

Lipson's method comprises:

(a) providing a polynucleotide complementary to an intronic sequence of a target gene…

See abstract and page 9775, column 1, "Probes" and figure 1.

(b) hybridizing the polynucleotide to intronic RNA or a nucleic acid produced therefrom to form a complex…

Lipson hybridized the probe to a Southern blot of an RT-PCR product derived from total cellular RNA (see "Results" section, figures 2-4, and table 1).

(c) quantitatively detecting the complex to produce expression data

Lipson quantitatively detected the complex formed by autoradiography and densitometry (see figures 2-4 and table 1).

(d) determining the expression level of the target gene based on the expression data

Lipson determined, for example, that "[t]he expression of TK hnRNA at 16 hr was >10-fold greater than in G_o cells" (page 9776, column 1, 1st paragraph). See also the quantitative data in table 1.

With regard to claim 110, Lipson immobilized the polynucleotide (the RT-PCR product) on a solid surface (a membrane; see page 9775, column 1, "Southern Blotting"). The Southern blot can be considered an array. There is no explicit definition of "array" in the specification. There is an explicit definition of "microarray" (paragraph [0129] of the published application): "The term "microarray" refers to an ordered arrangement of hybridizable array elements, preferably polynucleotide probes, on a substrate." Lipson's Southern blot is consistent with this definition.

With regard to claim 112, Lipson's target was human TK gene.

With regard to claim 113, Applicant's definition of an oligonucleotide as "a relatively short polynucleotide" (paragraph [0131] of the published application) is not a limiting definition and does not distinguish over Lipson's RT-PCR product.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 104-109 and 111-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Danenberg et al (US 2002/0009795) in view of Duvick (US 7.026,123, prior art of record), Clement et al (Journal of Biological Chemistry, 276(20)16919-30 (2001), cited on the IDS of 05/20/2005), Lipson et al (PNAS 86:9774-7 (1989)), Chang et al (Journal of Neuroscience Methods 94:177-85 (2000)) and Matsubara et al (Endocrinology 138(11):5075-8 (1997)).

Danenberg teaches (paragraph [0004]): "The determination of gene expression levels in tissues is of great importance for accurately diagnosing human disease and is increasingly used to determine a patient's course of treatment."

Danenberg teaches (paragraph [0007], citations omitted): "Previous studies have shown that the levels of TS [thymidylate synthase] protein directly correlate with the effectiveness of 5-FU therapy, that there is a direct correlation between protein and RNA expression and that TS expression is a powerful prognostic marker in colorectal and breast cancer."

Danenberg teaches (paragraph [0009]): "Until now, quantitative tissue gene expression studies including those of TS expression have been limited to reverse transcriptase polymerase chain reaction (RT-PCR) amplification of RNA from frozen tissue. However, most pathological samples are not prepared as frozen tissues, but are routinely formalin-fixed and paraffin-embedded (FFPE) to allow for histological analysis and for archival storage...Because paraffin-embedded samples are widely available, rapid and reliable methods are needed for the isolation of nucleic acids, particularly RNA, from such samples."

Danenberg teaches (paragraph [0014]) a method that "provides simple, efficient and reproducible methods for the isolation of RNA, DNA or proteins from tissue that has been embedded in paraffin."

Danenberg teaches (paragraph [0022]): "Purified RNA can be used to determine the level of gene expression in a formalin-fixed paraffin-embedded tissue sample by reverse transcription, polymerase chain reaction (RT-PCR) amplification. Using appropriate PCR primers the expression level of any messenger RNA can be determined by the methods of the invention. The quantitative RT-PCR technique allows for the comparison of protein expression levels in paraffin-embedded (via

immunohistochemistry) with gene expression levels (using RT-PCR) in the same sample."

Danenberg teaches (paragraph [0034]): "Moreover, the technique can be applied to any of a wide range of tumor types and to an unlimited range of target genes. This has implications for the future preparation of individual tumor "gene expression profiles" whereby expression levels could be determined in individual patient samples for a range of genes that are known to influence clinical outcome and response to various chemotherapeutic agents. Automated real-time PCR from FFPE sample allows for the targeting of treatment to individual tumors."

Taken together, these teachings suggest a method of determining the expression level of a target gene in a formalin-fixed paraffin-embedded breast cancer tissue sample obtained from a human subject, providing a polynucleotide complementary to the target gene (in the form of primers, i.e. oligonucleotides, for quantitative RT-PCR), hybridizing the polynucleotides to RNA corresponding to the target gene to form a complex, quantitatively detecting the complex (by quantitative RT-PCR) to produce expression data, and determining the expression level of the target gene based on the expression data, as recited in claims 104, 106-108 and 111-113. In addition, Danenberg's teachings suggest determining if the expression level correlates with a clinical outcome, as recited in claim 105.

With regard to claim 109, Danenberg determines a normalized expression level of a target gene (TS) relative to the expression level of one or more reference genes (β-actin) in the tissue sample (see figure 7, paragraphs [0030] and [0052]).

The only thing Danenberg does not teach is that the primers (and detection probe; see paragraph [0052]) were specific for intron sequences.

Duvick teaches methods for examining the effects of transforming clones of nucleic acid sequences into host cells, where each clone comprised a candidate sequence and a "U-tag", a short, random nucleotide sequence (see column 5, lines 17-28). Duvick teaches that the U-tag may "be designed into an intron sequence that occurs anywhere within a transcript" (column 5, lines 59-60). Duvick states (column 5, line 65, citing Clement): "In this design, the spliced-out intron RNA would be detected at a level proportional to the transcription rate. Recent data from mammalian cells indicates that intron RNAs, after splicing, persist in the cell with reasonable half-lives, contrary to what was previously thought." The point is that Duvick suggests that introns can be detected, and that the level of the detected intron correlates with transcription rate (i.e. expression).

Clement states:

> "A widely held belief is that spliced introns accumulate at low levels because they are rapidly degraded (within seconds) at their site of origin in the nucleus (14, 22). However, there is little direct evidence to support this view. The only mammalian intron whose fate and stability have been examined in detail is the $IVSI_{c\beta1}$ intron from a mouse T-cell receptor $(TCR)^1$-β gene. This intron is easily detectable by the relatively insensitive Northern blot procedure, despite being generated from only a modestly transcribed gene (23)." (1^{st} full paragraph, page 16920)

> "Because the Pem gene is not cell type-specific and its introns appear to be typical, we hypothesized that Pem would be a good candidate to provide information on the metabolism of mammalian introns in general." (2^{nd} full paragraph, page 16920)

> "Our analysis of the three introns in the Pem coding region revealed that they had a range of half-lives that were even longer than that of the only other previously analyzed vertebrate intron, $IVSI_{c\beta1}$." (3^{rd} full paragraph, page 16920)

Thus Clement teaches that introns from the Pem gene, which appear to be typical introns, are more stable (longer half-lives) than the $IVSI_{CB1}$ intron, which was detectable by the "relatively insensitive Northern blot procedure".

Lipson teaches detecting levels of TK (human thymidine kinase) expression by subjecting total RNA to RT-PCR and detecting the resulting product on a Southern blot. See entire article, especially figures 1 and 2.

Matsubara teaches quantitative analysis of GH (growth hormone, rat) pre-mRNA expression using an intron-specific competitive PCR method (see page 5076, figure 1 and column 1).

Chang teaches a method of analyzing tyrosine hydroxylase (rat) transcription using an intron specific probe by RNase protection (see section 2.2, page 178) and in situ hybridization (see section 2.4, page 180). Chang cites other studies that have successfully used intron-specific in situ hybridization to detect rat vasopressin/neurophysin I, corticotrophin releasing hormone, neurotensin, and gonadotropin releasing hormone (see second paragraph, section 4, page 184). Chang notes (last paragraph, page 184, citations omitted, emphasis provided):

> Based on the present results, together with previous work on the expression of neuropeptide genes, we conclude that estimates of transcription rates for the TH gene based on relative levels of intron 2 sequences are well founded. The logical extension and underlying rationale of the present study is the application of intron-specific in situ hybridization analysis for studies on TH gene expression within neural tissues where nuclear run-on assays or RNase protection are not possible because of reasons of sensitivity or that the preservation of anatomical information is important.

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the method suggested by Danenberg by measuring expression based on the detection of intron sequences as suggested by Duvick. In fact the disclosures of Lipson,

Matsubara and Chang all use intron-specific primers or probes to quantify gene expression. The disclosures of Clement, Lipson, Matsubara and Chang provide a reasonable expectation of success in quantitatively detecting intron sequences as a measure of gene expression. Based on the disclosures of Clement, Lipson, Matubara and Chang, one of skill in the art would have had a reasonable expectation of success in detecting intron sequence, a reasonable expectation of success that the levels of detected intron sequence would be proportional to the transcription rate, which is a measure of gene expression, and a reasonable expectation of success in quantitatively detecting the sequences given the quantitative densitometry taught by Lipson and the quantitative PCR taught by Masubara. Furthermore, one would have had a reason to use intron sequences because based on the disclosures of the cited references, intron sequences would have been clearly obvious alternatives to exon sequences in measuring gene expression.

Response to Arguments

Applicant's arguments filed 12/03/2008 have been fully considered but they are not persuasive. Applicant argues (page 6) that:

> in order for the claimed method to be a predictable success, one of ordinary skill in the art would have to have possessed knowledge that: a) intron sequences could be detected *and* b) that the level of intron sequence is correlative with the amount of mature mRNA of the target gene.

With regard to (a), the cited art clearly shows that intron sequences could be detected. With regard to (b), the claims do not recite anything about the level of intron sequence correlating with the amount of mature mRNA. Moreover, the phrase

"expression level of a target gene" (recited in claim 104) is not defined in the specification. Since the claims are directed to detecting intron sequences, then what is being detected by the claimed method is just that: intron sequence, either spliced out "free introns" or introns within primary transcripts (pre-mRNA) or incompletely spliced heterogeneous nuclear RNA (hnRNA) (see Chang, paragraph spanning pages 177-178, where Chang teaches that "the nuclear level of intron-containing RNA sequences also can serve as an index of transcriptional activity of a given RNA"). Chang also states (last paragraph, page 184) that "estimates of transcription rates for the TH gene based on relative levels of intron 2 sequence are well founded" and that the "logical extension…is the application of intron-specific in situ hybridization for studies on TH gene expression". While it is appreciated that "gene expression" can be measured in a number of ways (e.g. steady-state level of protein, rate of translation, steady-state level of mature RNA, steady-state level of intronic, "pre-mRNA" or "hnRNA", rate of transcription), Applicant's methods detect intronic RNA, and this is what Duvick suggested and what Clement, Lipson, Matsubara and Chang actually did.

Applicant's arguments and cited references teaching that intronic RNA was thought to be rapidly degraded have been considered. However, regardless of how rapidly intronic RNA is degraded, the art cited in the rejection (as well as additional studies cited within the references relied upon) indicates that detection of intronic RNA was clearly possible. Furthermore, the art cited in the rejection taught that levels of intron-containing RNA (pre-mRNA, hnRNA) correlated with transcription rate (the first step in gene expression).

Applicant's comments regarding the Thomas reference (pages 8-9 of the response) are noted. However, the current rejection does not rely on Thomas.

In summary, intron-containing nucleic acids were routinely detected in the prior art using intron-specific primers or probes, the prior art enabled quantitative measurement of such sequences, the levels of intron-containing RNA were considered to reflect the rate of transcription, which can be considered an "expression level of a target gene", and Duvick suggested detecting intronic sequences as correlating with transcription rate. Therefore it would have been obvious to target intronic sequences as an alternative to exon sequences to measure gene expression.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637